Are heart doses associated with survival in patients with non-small cell lung cancer who received post-operative thoracic radiotherapy?

A national population-based study

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Abstract

The aim of this retrospective national cohort study is to assess the association between various radiation heart dosimetric parameters (RHDPs), acute myocardial infarct (AMI) and overall survival (OS) outcomes in non-small cell lung cancer (NSCLC) patients treated with post-operative thoracic radiotherapy (PORT) using contemporary radiation techniques.

We identified patients with stage I to III NSCLC treated with PORT at the 2 national cancer institutions from 2007 to 2014. We linked their electronic medical records to the national AMI and death registries. Univariable Cox regression was performed to assess the association between various RHDPs, AMI, and OS.

We included 43 eligible patients with median follow-up of 36.6 months. Median age was 64 years. Majority of the patients had pathological stage III disease (72%). Median prescription dose was 60Gy. Median mean heart dose (MHD) was 9.4Gy. There were no AMI events. The 5-year OS was 34%. Univariable Cox regression showed that age was significantly associated with OS (hazard ratio, 1.06; 95% confidence interval, 1.01 to 1.10; P = .008). Radiation heart doses, including MHD, volume of heart receiving at least 5, 25, 30, 40, 50Gy and dose to 30% of heart volume, were not significantly associated with OS.

There is insufficient evidence to conclude that RHDPs are associated with OS for patients with NSCLC treated with PORT in this study. Studies with larger sample size and longer term follow-up are needed to assess AMI outcome.

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy, AMI = acute myocardial infarct, CT = computed tomography, CTV = clinical target volume, EQD2 = biological equivalent doses in 2Gy fractions, Gy = Gray, IMRT = intensity-modulated radiotherapy, MHD = mean heart dose, NSCLC = non-small cell lung cancer, OS = overall survival, PET = positron emission tomography, PORT = post-operative thoracic radiotherapy, PTV = planning target volume, RHDPs = radiation heart dosimetric parameters.

Keywords: myocardial infarct, non-small cell lung cancer, post-operative thoracic radiotherapy, radiation dosimetry

1. Introduction

The National Comprehensive Cancer Network and European Society of Medical Oncology guidelines recommend the use of post-operative thoracic radiotherapy (PORT) in selected patients with non-small-cell lung cancer (NSCLC).[14,21] PORT has been shown to reduce local recurrence and potentially improve overall survival (OS) in patients with positive surgical margins or pathological N2 disease.[4,5,9,19,20,23] However, a recent update of a Cochrane meta-analysis reported its detrimental effect on OS in completely-resected NSCLC.[6] As such, there remains equipoise in this scenario and this is being investigated by the ongoing European large multi-institutional randomized trial (Lung ART).[13]

Lally et al evaluated 6148 patients retrospectively and showed that PORT was significantly associated with increased risk of cardiac mortality on multivariable analysis.[18] The detrimental effects of PORT in the early studies were largely attributed to the older radiation techniques used, which are likely to cause more treatment-related toxicities.[10,12] Technological advancement in radiation therapy such as conformal dose delivery using 3-dimenstional techniques and intensity-modulated radiotherapy (IMRT) have the potential to reduce the excess deaths from intercurrent disease that had previously negated the survival benefit of PORT. The secondary analysis of RTOG 0617 and other studies suggested that radiation heart dosimetric parameters (RHDPs) were potentially associated with cardiac toxicity and OS in patients with locally-advanced NSCLC treated with definitive thoracic radiotherapy (RT).[7,11,24,26,27] However, it remains unclear if these associations are applicable to patients receiving modern PORT treatment.

Therefore, we aim to perform a retrospective cohort study to assess the association between RHDPs, acute myocardial infarct (AMI) and OS outcomes in patients with NSCLC who received PORT using national-level data.

2. Materials and methods

2.1. Study design

This was an institutional review board approved retrospective cohort study of 2 national cancer institutions in Singapore.

2.2. Study population

Patients with histologically-confirmed stage I to III NSCLC who were treated with lobectomy or pneumonectomy followed by PORT in 3 public institutions, namely National Cancer Centre Singapore (NCCS) and National University Cancer Institute, Singapore (NCIS) from January 2007 to December 2014 were included. PORT was recommended for patients with positive margins or pathological N2 disease. The patients were restaged using American Joint Committee on Cancer eighth edition staging system.[15] The use of brain imaging with magnetic resonance or contrasted computed tomography (CT) and positron emission tomography-CT (PET-CT) for staging were recommended but not mandated. Post-operative lung function test was performed for all patients. Forced expiratory volume in one second (FEV1) should be more than 1.2L. Patients who received palliative, preoperative, definitive stereotactic body RT or re-irradiation to thorax were excluded.

2.3. Radiation treatment

Patients were simulated in the supine position, with both arms above the head on a pre-molded vac-lock. A CT simulation scan was performed with 2 to 3 mm-thickness slices from C5/6 to L2/3 vertebral levels. Intravenous contrast was used during CT simulation in NCCS; but optional in NCIS. Four dimensional (4D)-CT simulation were utilized depending on clinician's discretion.

During treatment planning, the pre-operative CT or PET-CT diagnostic images, when available, were reviewed and/ or fused with the CT simulation scan to guide target volume delineation. Operation and histology reports were used to determine the sites of disease. Clinical target volume (CTV) was contoured to cover the areas of resected tumor and the areas at risk for microscopic residual disease, including the tumor bed and bronchial stump. Planning target volume (PTV) was contoured by adding margins to CTV to account for organ motions and set-up uncertainties. The volume delineation and dose prescription in the respective institutions were detailed in Table 1. The dose constraints for each organ at-risk were shown in Table 2.

Treatment was delivered using 6-megavoltage photons via 3 dimensional- conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) or Arc therapy. Radiation was delivered one fraction per day, five fractions per week from Monday to Friday.

All the treatment volumes and plans were reviewed in quality assurance audit meeting during first week of radiotherapy. Orthogonal images were acquired for the first 3 fractions, and registered with the planning images. Electronic portal imaging was reviewed in the first week of treatment. Cone beam CT was used daily routinely since its implementation in 2012 in NCIS.

Table 1

Volume Delineation and Dose Prescription.

		National Cancer Centre Singapore	National University Hospital and Tan Tock Seng Hospital	
CTV	CTV-T	Tumor bed + bronchial stump + residual disease (if any)	CTV	Tumor bed + bronchial stump + residual disease (if any)
	CTV-N	Areas of positive nodes		
PTV	PTV-T	CTV-T + 7-mm margin in axial plane and 12-mm margin in longitudinal plane	PTV	CTV + 5 to 10-mm margin
	PTV-N	CTV-N + 5 mm margins in all directions		
Total dose prescribed		• 50Gy • 10 to 16Gy boost to areas of positive margin		• 50.4 to 54Gy • 6 to 10Gy boost for positive margins
Dose per fraction		• 2Gy		• 1.8 to 2Gy

CTV = clinical target volume, N = node, PTV = planning target volume, T = tumour.

Table 2

Dose constraints for organs at-risk.

Organs at-risk	Dose Constraints	Reference
Spinal Canal	$D_{max} \leq 50Gy$	QUANTEC[20]
Lungs	$D_{mean} \leq 20Gy$	QUANTEC[21]
	$V_{20} \leq 35\%$	
	$V_5 \leq 65\%$	
Heart	$D_{mean} \leq 40Gy$	RTOG 0617[22]
	$V_{60} \leq 33\%$	
	$V_{40} \leq 80\%$	
	$V_{45} \leq 60\%$	
	$V_{60} \leq 33\%$	
Esophagus	$D_{mean} \leq 34Gy$	RTOG 0117[23]
	$V_{55} \leq 30\%$	
	$D_{max} \leq 105\%$ of prescribed dose	RTOG 0813[24]
Brachial Plexus (for apical tumors)	$D_{max} \leq 66Gy$	RTOG 0617[22]

QUANTEC = quantitative analyses of normal tissue effects in the clinic.

PORT was delivered with or without chemotherapy, either concurrently or sequentially. Platinum-based doublet chemotherapy was preferred.

2.4. Dosimetric analysis

All previous radiation plans underwent dose calculation using Monte Carlo or Analytical Anisotrophic Algorithm. To account for variable fractionation schemes, biologically equivalent doses in 2-Gy fractions (EQD2) were calculated using the linear quadratic model (assuming α/β ratio = 10 for tumor control, α/β ratio = 2.5 for heart and α/β ratio = 3.0 for lungs). Dose-volume histograms were generated for review. RHDPs for analysis were prespecified based on the previous studies,[7,11,24,26,27] including heart mean dose (MHD), heart V5, heart V25, heart V30, heart V40, heart V50, dose to 30% of heart volume (heart D30), lung mean dose, lung V5 as well as lung V20. The lung volume was defined as left lung plus right lung minus PTV as per Lung ART protocol.[13]

2.4.1. Co-variates. Clinical data was collected from the institutional electronic medical records. Gender (male or female), Eastern Cooperative Oncology Group (ECOG) performance status (2 or 0/1), smoking status (current/ former or never), diabetes mellitus (DM) (yes or no), pre-existing ischemic heart disease (IHD) (yes or no), chronic obstructive pulmonary disease (COPD) (yes or no), use of PET-CT (yes or no), use of brain imaging (yes or no), tumor laterality (left or right), radiation technique (IMRT/ Arc therapy or 3D-CRT) and use of chemotherapy (yes or no) were analyzed as dichotomous variables. DM was defined as fasting plasma glucose of at least 7.0 mmol/L, a 2-hour post oral glucose tolerance test value of at least 11.1 mmol/L, or glycated hemoglobin value of at least 6.5%.[29] Pre-existing IHD was defined as the presence of AMI, coronary artery bypass grafting, or coronary angioplasty prior to the start of PORT. This data was captured from the national AMI registry as described below.[2] COPD was defined as a FEV1/ forced vital capacity ratio of less than 0.7 or less than the lower limit of normal plus and FEV_1 less than 80% predicted.[22] Histology was categorized into adenocarcinoma, squamous cell carcinoma and others. Lobar location of tumor was categorized

into upper lobe, middle lobe, lower lobe and multiple lobes. Resection margin was categorized into R0 (free margin), R1 (microscopic residual margin) and R2 (macroscopic residual margin).[17] Age and RHDPs were analyzed as continuous variables.

2.5. Endpoints

The co-primary endpoints were AMI and OS. The unique national identification number assigned to all Singapore residents was used to link the study's cohort to the national AMI and death registries. The national AMI registry was established in 1988 to collect epidemiological data on AMI cases diagnosed in all the public hospitals.[2] AMI cases diagnosed in private hospitals were included since 2012. The registry receives notifications on AMI cases from all hospitals, Ministry of Health and Ministry of Home Affairs. The International Classification of Diseases (ICD)-9 Clinical Modification code 410 was used to identify AMI cases in the data sources from 2007 to 2011, while the ICD-10 Australian Modification codes I21 and I22 were used from 2012 onwards. All the cases of AMI are diagnosed by certified doctors, with the evidence of symptoms of AMI, elevation of cardiac enzymes or abnormal electrocardiogram. Death status was obtained from the national death registry which contains information on the date and cause of deaths for all Singapore residents.

2.6. Statistical analysis

Frequency with percentage and median with interquartile range were used to describe the baseline characteristics of this study cohort. The pre-planned univariable analysis of AMI for its association with baseline characteristics was not performed due to the absence of AMI events in this study. Time to all-cause death was measured from the time of first day of radiotherapy treatment to death from any cause. Univariable Cox regression analysis was performed to determine the association between baseline characteristics and all-cause death. For all analyses, 2-sided P values of less than .05 were considered statistically significant. Analyses were performed using STATA (version 13.0, StataCorp).

3. Results

3.1. Baseline characteristics of study population

The baseline characteristics of the 43 study patients were summarized in Table 3. The median follow-up duration was 36.6 months (interquartile range, 11.9 to 55.1). The date of last censorship was set at 30 November 2017. The median age was 63.6 years (interquartile range, 54.2 to 67.0). The 58% of the study population were female and 67% never smokers. Nearly all of them had good ECOG performance status (95%). Majority of them were not diabetic (84%) and did not have pre-existing IHD (86%) or COPD (98%) and did not use PET-CT for staging (56%). Most of them had brain imaging, in the form of MR or contrasted CT (81%) for initial staging. Adenocarcinoma was the commonest tumor histology (72%). The tumor was located more on the right side (63%) and in the upper lobe (58%). The commonest T and N stages were T2 (44%) and N2 (67%). 35% of the study population had R1 or R2 resection. Most of them received concurrent or sequential chemotherapy (72%). The

Table 3

Baseline characteristics of study population.

Characteristics	n = 43
Sociodemographic and Clinical Characteristics	
Age at lung cancer diagnosis, year, median (IQR)	63.6 (54.2–67.0)
Gender	
Female	25 (58.1%)
Male	18 (41.9%)
ECOG performance status	
0 and 1	41 (95.4%)
2	2 (4.6%)
Smoking status	
Never smoker	29 (67.4%)
Current and former smoker	14 (32.6%)
Diabetes mellitus	
No	36 (83.7%)
Yes	7 (16.3%)
Pre-existing ischemic heart disease	
No	37 (86.0%)
Yes	6 (14.0%)
Chronic obstructive pulmonary disease	
No	42 (97.7%)
Yes	1 (2.3%)
Use of PET-CT for staging	
No	24 (55.8%)
Yes	19 (44.2%)
Use of brain imaging (MRI or contrasted CT) for staging	
No	8 (18.6%)
Yes	35 (81.4%)
Tumor Characteristics	
Histology	
Adenocarcinoma	31 (72.1%)
Squamous cell carcinoma	5 (11.6%)
NSCLC NOS	7 (16.3%)
Tumor laterality	
Left	16 (37.2%)
Right	27 (62.8%)
Lobar location of tumor	
Upper	25 (58.1%)
Middle	5 (11.6%)
Lower	13 (30.2%)
Pathological T stage	
T1	15 (34.9%)
T2	19 (44.2%)
T3	6 (13.9%)
T4	3 (7.0%)
Pathological N stage	
N0	10 (23.3%)
N1	4 (9.3%)
N2	29 (67.4%)
Overall pathological stage	
Stage I	3 (7.0%)
Stage II	9 (20.9%)
Stage III	31 (72.1%)
Resection margin status	
R0	28 (65.1%)
R1	13 (30.2%)
R2	2 (4.7%)
Treatment Characteristics	
Use of concurrent or sequential chemotherapy	
Yes	31 (72.1%)
No	11 (25.6%)
Unknown	1 (2.3%)
Type of chemotherapy used	
Cisplatin + vinorelbine	13 (30.2%)

(continued)

Table 3

(continued).

Characteristics	n = 43
Cisplatin + gemcitabine	6 (14.0%)
Cisplatin + pemetrexed	4 (9.3%)
Carboplatin + vinorelbine	2 (4.7%)
Carboplatin + gemcitabine	2 (4.7%)
Carboplatin + pemetrexed	2 (4.7%)
Carboplatin + paclitaxel	2 (4.7%)
Thoracic radiation technique	
3D-CRT	30 (69.8%)
IMRT or Arc therapy	13 (30.2%)
Prescribed thoracic radiation dose, Gy, median (IQR)[*]	60.0 (50.0–60.0)
Dosimetric Characteristics	
Mean heart dose, Gy, median (IQR)	9.4 (2.3–14.6)
Heart volume received $\geq$ 5 Gy (Heart V5), percentage, median (IQR)	34.0 (9.7–46.0)
Heart volume received $\geq$ 25 Gy (Heart V25), percentage, median (IQR)	15.0 (2.0–24.0)
Heart volume received $\geq$ 30 Gy (Heart V30), percentage, median (IQR)	12.3 (1.0–20.0)
Heart volume received $\geq$ 40 Gy (Heart V40), percentage, median (IQR)	4.6 (0.0–14.5)
Heart volume received $\geq$ 50 Gy (Heart V50), percentage, median (IQR)	2.0 (0.0–6.0)
Dose to 30% of heart volume (Heart D30), Gy, median (IQR)	7.4 (1.5–17.5)
Mean lung dose, Gy, median (IQR)	11.2 (10.1–13.6)
Lung volume received $\geq$ 5 Gy (Lung V5), percentage, median (IQR)	48.0 (40.0–56.0)
Lung volume received $\geq$ 20 Gy (Lung V20), percentage, median (IQR)	20.4 (16.0–26.0)
PTV in 10 cc, median (IQR)	20.8 (15.1–38.8)

3D-CRT = 3-dimensional conformal radiation therapy, ECOG = Eastern Cooperative Oncology Group, IMRT = intensity-modulated radiation therapy, IQR = interquartile range, MRI = magnetic resonance imaging, NSCLC NOS = non-small-cell lung cancer not otherwise specified, PET-CT = positron emission tomography-computed tomography, PTV = planning target volume.

[*] All doses are in equivalent dose in 2-Gy fraction.

most frequently used radiation technique was 3D-CRT (70%). The median total prescription dose was 60Gy. 49% of patients received 50.4 to 54Gy at 1.8 to 2Gy per fraction; 46% received 60 to 66Gy at 2Gy per fraction; while 5% received 70Gy at 2Gy per fraction (for 2 patients with residual macroscopic disease). The median mean heart dose was 9.4Gy. The median heart V5, V25, V30, V40, V50, and D30 were 34%, 15%, 12%, 5%, 2%, and 7.4Gy, respectively. The median mean lung dose was 11.2Gy. The median lung V5 and V20 were 48% and 20%. The median PTV was 208 cc. There were no AMI events.

3.2. Univariable Cox regression analysis on factors associated with OS

The total number of deaths from any cause was 27. The median survival duration was 23.4 months. The 2-year and 5-year OS were 65% and 34%. Univariable Cox regression analysis showed that age (hazard ratio, 1.06; 95% confidence interval, 1.01 to 1.10; P = .008) was the only factor significantly associated with OS, with the older people having an increased risk for all-cause death (Table 4). The various RHDPs, including MHD, heart V5, V25, V30, V40, V50, and D30, were not significantly associated with OS.

Table 4

Univariable Cox Regression Analysis: Characteristics Associated with All-Cause Death outcome.

Characteristics	All-Cause Death Outcome		
	HR	95% CI	*P* value
Sociodemographic Characteristics			
Age at lung cancer diagnosis, year	1.06	1.01–1.10	.008
Male (vs female)	1.34	0.62–2.88	.456
ECOG 2 (vs 0 and 1)	0.65	0.09–4.82	.674
Clinical Characteristics			
Current and former smoker (vs never smoker)	1.47	0.65–3.30	.354
Diabetes mellitus	1.96	0.77–4.98	.155
Pre-existing ischemic heart disease	2.04	0.76–5.50	.159
Chronic obstructive pulmonary disease	1.79	0.24–13.40	.572
Use of PET-CT for staging	1.07	0.49–2.35	.860
Use of brain imaging (MRI or contrasted CT) for staging	1.28	0.44–3.71	.648
Tumor Characteristics			
Histology (vs adenocarcinoma)			
Squamous cell carcinoma	2.69	0.97–7.50	.058
NSCLC NOS	0.72	0.21–2.44	.596
Left-sided tumor (vs right-sided)	1.37	0.63–2.99	.428
Lobar location of tumor (vs upper)			
Middle	0.20	0.03–1.53	.121
Lower	1.44	0.65–3.18	.371
Pathological T stage (vs T1)			
T2	1.12	0.46–2.75	.805
T3	1.88	0.56–6.37	.309
T4	3.70	0.94–14.61	.062
Pathological N stage (vs N0)			
N1	0.99	0.25–3.87	.992
N2	0.69	0.28–1.67	.406
Overall pathological stage (vs stage I)			
Stage II	1.34	0.27–6.69	.721
Stage III	1.10	0.25–4.78	.898
Resection margin status (vs R0)			
R1	1.48	0.66–3.28	.339
R2	1.11	0.15–8.40	.922
Radiation and Systemic Treatment Characteristics			
Use of concurrent or sequential chemotherapy	0.92	0.40–2.12	.853
IMRT or Arc therapy (vs 3D-CRT)	0.43	0.16–1.14	.090
Prescribed thoracic radiation dose, Gy[*]	1.00	0.94–1.07	.904
Dosimetric Characteristics			
Mean heart dose, Gy	0.99	0.94–1.05	.817
Heart volume received ≥ 5 Gy (Heart V5), %	1.00	0.98–1.01	.551
Heart volume received ≥ 25 Gy (Heart V25), %	1.00	0.97–1.02	.780
Heart volume received ≥ 30 Gy (Heart V30), %	1.00	0.97–1.03	.855
Heart volume received ≥ 40 Gy (Heart V40), %	1.00	0.96–1.04	.975
Heart volume received ≥ 50 Gy (Heart V50), %	1.01	0.93–1.09	.868
Dose to 30% of heart volume (Heart D30), Gy	1.00	0.96–1.03	.918
Mean lung dose, Gy	0.98	0.88–1.09	.705
Lung volume received ≥ 5 Gy (Lung V5), %	0.99	0.97–1.02	.655
Lung volume received ≥ 20 Gy (Lung V20), %	0.98	0.93–1.03	.393
PTV, 10 cc	1.02	0.99–1.04	.170

3D-CRT = 3-dimensional conformal radiation therapy, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, IMRT = intensity-modulated radiation therapy, MRI = magnetic resonance imaging, NSCLC NOS = non-small-cell lung cancer not otherwise specified, PET-CT = positron emission tomography-computed tomography, PTV = planning target volume.

[*] All doses are in equivalent dose in 2-Gy fraction

4. Discussion

In our study, there were no AMI events detected amongst the patients with NSCLC treated with PORT. This finding is promising despite the small sample size and relatively short follow-up. The patients in PORT cohort were likely very well-selected given that they were fit enough to undergo surgery. Most patients had excellent performance status and limited medical comorbidities. Our results were consistent with earlier studies with low incidences of cardiac morbidity and mortality ranging from 3% to 6%.[10,12,18] Lally et al reviewed 6148 patients with resected node-positive NSCLC and reported that the cardiac mortality rates in PORT and no PORT group were similar at 6%.[18] However, multivariable analysis showed that PORT significantly increased hazards for cardiac mortality compared to no PORT after being adjusted for age, gender, race and year of diagnosis, especially in those diagnosed in older years from 1983

to 1988.[18] Douillard et al performed a secondary analysis of the ANITA trial, a phase III randomized trial of adjuvant cisplatin and vinorelbine chemotherapy versus observation in 840 patients with completely-resected stage IB to IIIA NSCLC. The use of PORT was recommended for pathological node-positive disease but not randomized or mandatory in this trial. 232 patients received PORT. Three percent of the patients in PORT group died of acute myocardial infarct, congestive heart failure, thromboembolism and pulmonary failure, compared to 0.6% in no PORT group.[12] Dautzenberg et al performed a randomized trial of PORT in 728 patients with completely-resected NSCLC and reported that the excess mortality rate for PORT group was due to excess intercurrent deaths, in which the 5-year intercurrent death rates were 31% for PORT group and 8% for no PORT group. Five percent of the patients in PORT group had cardiac cause as the most common etiology of intercurrent death, compared to 1.7% of the patients in no PORT group.[10]

Overall, there were a number of limitations with these early studies, rendering the findings not applicable to current modern practice. First, the radiation techniques used in these studies were considered outdated. For instance, the study by Dautzenberg et al used the total prescribed dose of 60Gy for completely-resected tumors and the radiation field arrangements were antiquated.[10] Similarly, Cobalt-60 teletherapy and larger daily fractionation sizes were allowed in some of the trials in the PORT meta-analysis and these have been linked to increased normal tissue toxicity.[1] Second, the effects of RHDPs were not evaluated in these studies. Recent studies by Dess et al and Wang et al suggested an association between RHDPs (such as mean heart dose, heart V5, and V30) and adverse cardiac events in locally-advanced NSCLC treated with definitive thoracic RT.[11,27] We might be able to extrapolate similar findings to the context of PORT. However, the RHDPs prespecified in our study were primarily based on the definitive RT studies, where dose-escalation trials were also included and thus the corresponding radiation doses to the heart were likely higher. Future research is required to identify the relevant RHDPs associated with cardiac toxicity and even OS in patients undergoing PORT. Third, specific cardiac events were not assessed in the early studies. While cardiac mortality, as a frequently-measured endpoint in the older studies, could determine if the survival benefit conferred by PORT would eventually be offset, it should also be noted that the cardiac events are heterogenous in their own etiologies and potentially associated with distinct heart substructure doses as suggested by Wang et al in a study of 112 patients with stage III NSCLC treated with dose-escalation RT trial.[28]

The 5-year OS in our study was 34%, which was similar to the other studies. The 5-year OS in the studies by Lally et al,[19] Dautzenberg et al,[10] Douillard et al,[12] Billiet et al,[4] Robinson et al,[23] and Corso et al[9] were 30%, 30%, 33% (no chemotherapy group, versus 44.6% in chemotherapy group), 35.1%, 38.4%, and 47.2% (pathological N0, vs N1 39.1% and N2 29.3%), respectively. To the authors' knowledge, there was no prior study performed to assess the relationship between RHDPs and OS in NSCLC patients who received PORT. Our study found that various RHDPs were not significantly associated with OS. The secondary analysis of RTOG 0617 and a study by Speirs et al reported that heart doses (such as heart V40 and V50) were significantly associated with OS in patients with locally-advanced NSCLC treated with definitive thoracic RT.[7,24] Our

sample size was rather small and there might not be sufficient power to detect the differences in survival outcomes. Furthermore, as mentioned earlier, PORT cohort as a distinctive entity by its own, might not share the similar RHDPs in predicting OS.

Interestingly, the univariable analysis demonstrated that patients with left sided tumor had a 37% increase in the hazards of death compared to patients with right sided tumor. The increase in hazards of death was not statistically significant which could be due to limited sample size. It is very likely that patients with left sided tumor would have received higher dose to the cardiac structures, resulting in more deaths due to cardiac toxicity. Hardy et al demonstrated that the risk for ischemic heart disease and cardiac dysfunction was increased when radiation was rendered to the left lung in a large retrospective cohort study including 34,209 patients.[16]

The strengths of this study include first, this is the first study evaluating the association between RHDPs and OS in NSCLC patients received modern PORT. Second, the national AMI and death registries were used to measure the 2 co-primary endpoints. This has likely reduced the underreporting bias of cardiac events. Third, quality assurance audit was conducted for all the radiation volumes and plans, in which this has been made mandatory in the Lung ART protocol to minimize inter-clinician variations in volume contouring.[25]

Our study was limited by its small sample size and relatively short median follow-up duration of 3 years. This median follow up duration was slightly longer compared to Lally et al' study (2.1 years)[18] and much shorter compared to Dautzenberg et al's study (5.7 years).[10] Cardiac toxicity is traditionally recognized as one of the late radiation effects, especially well-established in the long-term survivors of breast cancer and lymphoma.[3,8] Despite the earlier onset of cardiac events observed in the studies on definitive thoracic RT in locally-advanced NSCLC,[11,27] longer term follow-up would probably permit the detection of late cardiac events in patients treated with PORT who tend to have better prognosis and survival.

In this study, using national-level cohort data, we did not find any statistical significance between RHDPs and OS. Though the AMI outcome could not be analyzed given the absence of AMI events, we believed that heart dosimetry should be stricter in PORT treatment as compared to definitive thoracic RT treatment because irradiation of bronchial stump and mediastinum is often inevitable in PORT treatment, whereby the heart which lies near is likely to have received higher radiation dose. We await the results of the accruing Lung ART trial and hope that it can further define the risk-benefit ratio of PORT in the era of contemporary radiation therapy.

5. Conclusions

In summary, there is insufficient evidence to conclude that RHPDs are associated with OS for patients with NSCLC treated with PORT. Studies with larger sample size and longer-term follow-up are needed to assess AMI outcome, given the possibility of late occurrence of AMI events.

Author contributions

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